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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/521,387	01/14/2005	Reiner Luttmann	SARTORIUS-12	2344

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EXAMINER	
HOBBS, MICHAEL L	

ART UNIT	PAPER NUMBER
1797	

MAIL DATE	DELIVERY MODE
06/12/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/521,387	LUTTMANN ET AL.	
	Examiner	Art Unit	
	MICHAEL HOBBS	1797	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 March 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment from 03/24/2008 has been considered and entered for the record. Applicant's amendment overcomes the rejections under 35 U.S.C. 112 second paragraph, the objection to the drawings and specification and said rejections and objections are withdrawn. Claims 1-21 are pending for further examination on the merits.

Response to Arguments

2. Applicant's arguments, see page 4 claim 1 and page 9 paragraph 2, filed 03/24/2008, with respect to claim 1 have been fully considered and are persuasive. The 102 rejection of claims 1, 2, 4, 8-10, 15-18 and 20 has been withdrawn.

3. Applicant argues on page 11 paragraphs 2 and 3 that Cornelissen does not disclose a second harvest receptacle for removing the cell-contaminated retentate from the bioreactor. While Cornelissen does not specifically teach sending the cell-contaminated retentate to a second harvest vessel, it would be an obvious modification to tap the retentate line to include a three-way valve to alter the flow between the bioreactor and a second harvest vessel.

Claim Rejections - 35 USC § 103

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

5. Claims 1, 3-21are rejected under 35 U.S.C. 103(a) as being obvious over Cornelissen et al. (CAB8-Computer Application in Biotechnology, June 25-27, 2001) in view of Andrews (US 5,346,826).

6. Cornelissen teaches an interated bioprocess for the production of recombinant proteins by cultivating Pichia Pastoris. For claim 1, Cornelissen teaches the step of using a device that includes bioreactor that cultivates cells which is connected to an upstream feed receptacle or glycerol feed (Fig. 3) and to a downstream cross-filtration or micro filtration unit (Fig. 3, page 1 section 2 paragraph 5). Cells and product are filtered by using a micro-filtration unit which has a retentate line connected to the bioreactor and a permeate line which connects to a product harvest vessel (Fig. 3). The process is monitored by various sensors which report back to a control unit (Fig. 4). Cornelissen does not teach using a second harvest vessel connected directly to the bioreactor.

7. Andrews discloses a process for growing prokaryotic or eukaryotic cellular material within a tubular membrane immersed in an aqueous solution where the membranes are part of the bioreactor (B5). Cells are sent from the bioreactor to a holding tank (HT15) for further growth and before being separated by a centrifuge (col. 13 lines 65-68). For claim 1, Andrews teaches using a holding tank to collect excess cells that are removed from the bioreactor. The removal of these cells improves the efficiency of the bioreactor and prevents fouling of the membrane within the reactor. The holding tank or second harvest vessel receives the cells directly from the bioreactor and holds the cells for further processing, i.e. additional growth or centrifuging.

Therefore, it would have been obvious to one of ordinary skill in the art to employ the step of using a holding tank as suggested by Andrews to remove cells from the bioreactor of Cornelissen. The suggestion for doing so at the time would have been in order to maintain the efficiency of the bioreactor (col. 13 lines 37-38) and to minimize fouling of the filter.

8. For claim 3, Cornelissen teaches the step where the **valuable product** is recombinant proteins (Abstract). For claim 4, Cornelissen does not specify that the process is conducted in a sequential and integrated manner, but does imply that the process steps happen in a specific sequence. Referring to Figure 1 of the OA, each phase of production leads to another phase which strongly implies that the production of recombinant DNA as taught by Cornelissen is sequential. Further, the automation of this process as shown in Figure 4 of Cronelissen shows that each part of the process is integrated or coupled and are part of the whole process (page 6 section 8 paragraph 1). Regarding the method of producing biotechnologically valuable products as in claim 5, Cornelissen teaches that the cells adapt to the medium and that the cells are propagated at a constant growth rate, μ, for the batch phase (page 3 sections 3 and 4, Fig. 2) and for claim 6 Cornelissen teaches the step of using an induction substance such as methanol during the production phase (page. 3 section 3 paragraph3) . For claim 7, Cornelissen teaches the step of using a flow diffusion analysis (FDA) to regulate a second feed receptacle (page 3 section 4, Fig. 3). With regards to claim 8, Cornelissen teaches that the product is harvested from the bioreactor by using a cross-flow filtration step (page 1 section 2 paragraph 5), but does not specify that the product

is harvested cell-free. However, since the cross-flow filtration step filters out the recombinant DNA produced within the bioreactor, it is an intrinsic property of the product that it would be cell-free.

9. Regarding claim 11, Cornelissen teaches the step where the yeast used to produce the **recombinant DNA** is Pichia pastoris (Abstract) and for claim 12, Cornelissen teaches the step where the inducing substance is methanol (page 3 section 4, Fig. 1 & Fig. 3). Regarding claims 13 and 14, Cornelissen teaches maintaining the methanol level at a constant level and that glycerol is fed to the bioreactor (page 3 sections 3 & 4, Fig. 3).

10. For claim 15, Cornelissen does not specify that the process is conducted in a continuous and integrated manner, but does imply that the process is continuous and integrated. Referring to Figure 1 of the OA, each phase of production leads to another phase which strongly implies that the production of recombinant DNA as taught by Cornelissen is continuous. Further, the automation of this process as shown in Figure 4 of Cronelissen shows that each part of the process is integrated or coupled with every step and device of the larger process (page 6 section 8 paragraph 1).

11. For claim 16, the fresh media refill and cell harvesting are carried out in parallel (page 3 section 4 paragraph 6).

12. With regards to claim 9, Cornelissen teaches that the cell harvesting and media refreshing phase happen in parallel, but does not specifically teach that the retentate is harvested. However, the retentate is sent back to the bioreactor for further processing and based on the teachings of Andrews discussed above, sending the retentate to a

holding tank would be within the skills of one of ordinary skill in the art. Therefore, it would be obvious to include the step of sending the cells to a holding tank as suggested by Andrews in order to control the weight within the bioreactor and minimize fouling the filter of Cornelissen.

13. For claim 10, Cornelissen teaches the step of sending the retentate back into the bioreactor (Fig. 3) and sending the permeate from the filter to the product harvest vessel (Fig. 3).

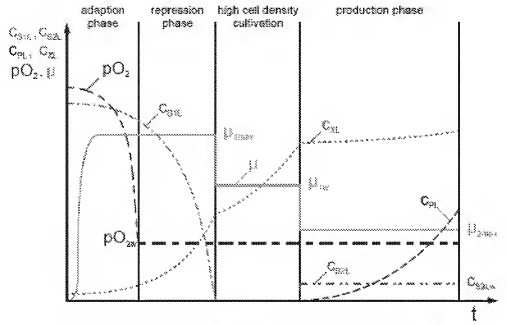

Fig. 2: Process course for automated production of recombinant proteins

Figure 1: Automated production of recombinant proteins (Cornelissen et al.)

14. Cornelissen teaches an interated bioprocess for the production of recombinant proteins by cultivating Pichia Pastoris. For claim 17, Cornelissen teaches a device that includes bioreactor that cultivates cells which is connected to an upstream feed

receptacle or glycerol feed (Fig. 3) and to a downstream cross-filtration or micro filtration unit (Fig. 3, page 1 section 2 paragraph 5). The micro-filtration unit is has a retentate line connected to the bioreactor and a permeate line which connects to a product harvest vessel (Fig. 3). The process is monitored by various sensors which report back to a control unit (Fig. 4). Cornelissen does not teach a second harvest vessel connected directly to the bioreactor.

15. Andrews discloses a process for growing prokaryotic or eukaryotic cellular material within a tubular membrane immersed in an aqueous solution where the membranes are part of the bioreactor (B5) used to cultivate the cells. Cells are sent from the bioreactor to a holding tank (HT15) for further growth and before being separated by a centrifuge (col. 13 lines 65-68). By using the holding tank, excess cells are removed from the bioreactor which improves the efficiency of the bioreactor and prevents fouling of the membrane within the reactor. Also, by using the holding tank with the bioreactor of Cornelissen, the cells from the bioreactor can be sent directly to the holding tank or secondary harvest vessel to await further processing and testing. Therefore, it would have been obvious to one of ordinary skill in the art to employ the holding tank as suggested by Andrews to remove cells from the bioreactor of Cornelissen. The suggestion for doing so at the time would have been in order to maintain the efficiency of the bioreactor (col. 13 lines 37-38) and to minimize fouling of the filter.

16. For claim 18, Cornelissen further teaches that the concentration of methanol is controlled by a feed pump that is connected to a control device (Fig. 3, page 3 section 4

paragraph 5) and for claim 19 the control device is a flow diffusion analysis (FDA) system (Fig. 3). For claim 21, a weight control on the bioreactor is connected to a feed pump for the product harvest vessel (Fig. 3).

17. With regards to claim 20, Cornelissen teaches that the cell concentration is measured by a sensor (Fig. 4-BIOSTAT ED) which is connected to a controller or computer (page 4 section 5 paragraph 3, Fig. 4- MFCS/win). Cornelissen teaches that sensors and a controller are connected to feed pumps, but remains silent regarding a pump up-stream of the second harvest vessel or holding tank.

18. Andrews teaches a holding tank as discussed above and does have a pump (P62) that is up-stream of the holding tank, but is used to re-circulate the cells back to the bottom of the bioreactor. However, it would be within the skills of one of ordinary skill in the art to move the pump to be in front of the valves on the line to the holding tank. The pump would be fully capable of re-circulating or sending the cells to the holding tank being positioned in front of the valve. Therefore, it would be obvious to one of ordinary skill in the art to employ the pump as suggested by Andrews in a position to draw cells from the bioreactor and send the cells to a holding tank. Refer to § MPEP 2144.01 VI A

19. Claim 2 is rejected under 35 U.S.C. 103(a) as being obvious over Cornelissen et al. (CAB8-Computer Application in Biotechnology, June 25-27, 2001) in view of Andrews (US 5,346,826) and in further view of Smith et al. (US 5,403,479).

20. Cornelissen and Andrews are silent regarding a cleaning and sterilizing step that happens *in situ*.

21. Smith teaches an *in situ* cleaning system for fouled membranes that includes using a cleaning solution and a biocidal solution. The types of membranes that are cleaned by the method disclosed by Smith include micro-filtration or ultra-filtration semi-permeable hollow fiber membranes. For claim 2, smith teaches introducing a cleaning solution in lieu of the feed where this cleaning solution is recycled over the entire surface of the membrane (col. 7 lines 20-25). Smith does not teach sterilizing and killing all bacteria within the hollow fiber membranes. However, the *in situ* cleaning method of Smith can be applied to the bioreactor of Cornelissen and Andrews to clean and sterilize the system with a reasonable expectation of success. Therefore, it would be obvious to incorporate the *in situ* cleaning methods as suggested by Smith in order to clean the filters of Cornelissen and Smith. The suggestion of doing so at the time would have been to remove any built-up bio-films that would inhibit the efficiency of the filters.

Conclusion

22. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MICHAEL HOBBS whose telephone number is (571)270-3724. The examiner can normally be reached on Monday-Thursday 7:30 AM - 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jill Warden can be reached on (571) 272-1267. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/William H. Beisner/
Primary Examiner, Art Unit 1797

MLH